SPECIFICATION

COMPOSITIONS FOR IMPROVING LIPID METABOLISM

TECHNICAL FIELD

The present invention relates to a pharmaceutical composition comprising lactoferrin and the like. The composition of the present invention can be used as an agent for improving lipid metabolism. More specifically, the composition of the present invention is useful for treating hypercholesterolemia, hyper-neutral lipidemia, hyper-low density lipoprotein (LDL) cholesterolemia, hypo-high density lipoprotein (HDL) cholesterolemia, obesity, fatty liver and cholesterol gallstone, and further for treating lifestyle-related diseases such as severe obesity, hyperlipidemia, hypertension and type II diabetes. The composition of the present invention can improve basal metabolic rate.

BACKGROUND ART

Our time is an age of plentiful food. With it, obesity has surfaced as an important health problem which has to be overcome. In the United State of America, about 30% of elementary school children are regarded as overweight children who exceed the standard weight by 30% or more. As is clear from various epidemiological surveys, the obesity of school age mostly proceeds after attaining manhood. With it, overweight persons who exceed the

lactic acid bacteria and the like which are necessary to maintain health. The side effects such as diarrhea, gas generation and abdominal distension recognized in the administration of orlistat reflect the change of an intestinal bacterial plexus in the large intestine.

DISCLOSURE OF THE INVENTION

The present inventors have found that when the lactoferrin to be obtained from cow milk is processed into enteric coated preparations of lactoferrin and orally administered to able-bodied persons and sick persons, the lipid metabolism can be quickly and significantly improved. Namely, on administering enteric preparations of lactoferrin to able-bodied persons and sick persons, the reduction in blood cholesterol level and blood neutral fat level, the rising in blood HDL cholesterol level and the reduction in blood LDL cholesterol level are caused with a statistically significant difference to accompany the improvement of the morbid condition such as essential hypertension and type II diabetes. Namely, clinical action to improve lipid metabolism is clear.

Further, it has been found that on investigations of the action to improve lipid metabolism with the use of rodents fed with a high fat feed, the cholesterol and the neutral fat in the liver are significantly reduced in addition to the same change of blood lipid as in humans. In other words, it has been found that lactoferrin inhibits the lipid accumulation in the liver by inhibiting

the absorption of dietary cholesterol and neutral fat by the digestive tract and has the action to improve the profile of blood lipid.

It is confirmed (Kawase et al., "Dairy Science and Food Study", vol. 45, A75 to 81, 1996) that oral administration of latoferrin to humans has an effect of increasing *Lactobacillus bifidus*. Even on oral administration of lactoferrin to humans, side effects such as diarrhea, gas generation and a feeling of abdominal distension which are seen with substances for inhibiting fat absorption have hardly been recognized. In other words, even when the fat which has escaped the digestion and absorption in the small intestine flows into the large intestine, the lactoferrin group protein proliferates useful intestinal bacteria such as *Lactobacillus bifidus*, and can be said to have an advantage of hardly causing harmful effects with the alternation of intestinal bacteria. In view of this, it has been thought that the lactoferrin group protein can be continuously used for a long period of time.

On the other hand, since yolk contains a large amount of cholesterol, hen eggs are misunderstood to induce arteriosclerosis and are unpopular food in Western countries in spite of its high nutritive value. However, unexpectedly, hen eggs have hardly any action to raise blood cholesterol level. For example, the experimental result of allowing six able-bodied volunteers to take in ten boiled eggs a day for many days in succession is

published, and a significant rising in blood cholesterol level did not occur even by taking in them for one week or more. Yolk contains a large amount of fats and oils and lecithin together with cholesterol, and the fats and oils are easily dispersed in water as fine micelles, and accordingly the absorption of cholesterol dissolved in the fats and oils by the digestive tract is expected to be quick. However, the reason why the blood cholesterol level does not rise even when a large amount of hen eggs are taken in over a long period of time is thought due to the possible presence of a substance which hinders the absorption of cholesterol by the digestive tract. The important matter is that even when a large amount of boiled eggs whose proteins are denatured, the inhibition of the rising in blood cholesterol level is recognized, and it was thought that a substance for inhibiting the absorption of cholesterol present in hen eggs is not affected by heating or active substance exists in the peptides to be formed by partial decomposition with digestive enzyme after denaturation although it might be a protein.

For example, the Poultry Association reported that the administration of egg white reduced the LDL cholesterol level in blood and raised the HDL cholesterol level in blood in the clinical test by adult able-bodied volunteers. Thus, it was thought that the substance to inhibit the rising in cholesterol level which existed in hen eggs existed in egg white. Nagaoka et al., Department

of Agriculture of Gifu University reported that when egg white was fractionated by taking the reduction in blood cholesterol in rodents as an indicator, the substance which exhibited activity was ovomucin (Information and Research on Stock Raising, Report, August, 2000, Monthly Report, Domestic Edition). However, the ovomucin in the egg white solids is around 4%, and thus considerable cost is required for commercialization by extracting ovomucin from egg white. Further, there is no clinical test to examine the variation of blood lipid by oral administration of ovomucin, and accordingly it is unknown whether the ovomucin is effective for a human or not.

By taking a hint from the action of lactoferrin to improve lipid metabolism, the present inventors investigated the absorption of fat and the influence on blood lipid by fractionating egg white to orally administer each fraction to rodents. This is based on the reason that egg white contains conalbumin corresponding to the mammalian lactoferrin and its content is around 10% or less next to ovalbumin. It is clear that the conalubumin of avian species is a protein corresponding to the lactoferrin of mammalian species by the comparison of the structures elucidated by the X-ray diffraction of the crystals (H. Kurokawa et al., J. Biol. Chem., 274:28445-28453, 1999). As the result of experiments, the present inventors have found that the conalbumin of the lactoferrin of avian species inhibits the absorption of dietary fat as expected to improve the profile of blood

lipid as with lactoferrin.

On the basis of such knowledge, the present inventors have completed a composition for improving lipid metabolism which has at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalubumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient and a composition for treating at least one disease or condition to be selected from the group consisting of hypercholesterolemia, hyper-neutral lipidemia, hyper-low density lipoprotein (LDL) cholesterolemia, hypo-high density lipoprotein (HDL) cholesterolemia, obesity, fatty liver and cholesterol gallstone which has at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalubumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient. The composition of the present invention is effective for treating lifestyle-related diseases such as severe obesity, hyperlipidemia, hypertension and type II diabetes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 represents graphs showing the rising in the protein concentration in blood by administration of

lactoferrin and the reduction in neutral at level and free fatty acid level (Example 1). The latticed bars on the left side show a control group and the dotted line bars on the right side show a lactoferrin group. The bars show standard deviations (each n=8). **P<0.01, in Student's t-test

Figure 2 is a graph showing a change in mouse blood cholesterol by administration of lactoferrin (Example 1). The latticed bars on the left side show a control group and the dotted line bars on the right side show a lactoferrin group. The bars show standard deviations (each n=8).

** P<0.01, in Student's t-test

Figure 3 shows a ratio of the HDL cholesterol level to the total cholesterol level in mouse blood (Example 1). The latticed bars on the left side show a control group and the dotted line bars on the right side show a lactoferrin group. The bars show standard deviations (each n=8). ** P<0.05, in Student's t-test

Figure 4 represents graphs showing a change in the lipid content in the liver by lactoferrin (Example 2). The latticed bars on the left side show a control group and the dotted line bars on the right side show a lactoferrin group. The bars show standard deviations (each n=8). *P<0.05 and **P<0.01, in Student's t-test

Figure 5 is a graph showing the effect of enteric coated tablets of lactoferrin on neutral fat level (Example 3). ● and ○ show the case of oral administration

of lactoferrin enteric tablets and ⊗ shows the case of no oral administration.

Figure 6 is a graph showing the effect of enteric coated tablets of lactoferrin on total cholesterol level (Example 4). $P<0.01$ in Student's paired t-test

Figure 7 is a graph showing the effect of enteric coated tablets of lactoferrin on waist and body weight.

Figures 8 to 11 show the effect of enteric coated tablets of lactoferrin on neutral fat level and total cholesterol level (Examples 5 to 8).

Figure 12 is graph showing the effect of enteric coated tablets of lactoferrin on neutral fat level and total cholesterol level in detail (Example 9). ● shows a measured value of neutral fat the next morning after drinking.

Figure 13A is a graph showing a lactoferrin concentration in blood when lactoferrin enteric tablets were orally administered (Example 10).

Figure 13B is a diagram showing the schedule of administration of enteric coated tablets of lactoferrin and collection of blood in measuring the lactoferrin concentration in blood.

Figure 14A is a graph showing the result of measuring the body temperature at rising and the body temperature one hour after lunch with a group administered with lactoferrin and Figure 14B is a graph showing that result with a control group (Example 11).

DETAILED DESCRIPTION OF THE INVENTION

The composition of the present invention has at least one of lactoferrin group proteins or enzymatically decomposed products of the lactoferrin group protein as an active ingredient. The "lactoferrin group protein" as used in the present specification includes lactoferrin and conalbumin, and the "enzymatically decomposed product of the lactoferrin group protein" includes a peptide corresponding to lactoffericin of the lactoferrin group protein.

For the composition of the present invention, any of the lactoferrin group protein and the enzymatically decomposed product of the lactoferrin group protein can be used as far as it exhibits the action to improve lipid metabolism and the action to basal metabolism rate on oral administration. Lactoferrin is a large molecule having a molecular weight of about 80,000 and has properties to form a chelate with two trivalent iron ions, and the "lactoferrin" as used in the present specification includes all types of lactoferrins ranging from the iron ion-free type to the type with iron ions completely saturated which can be human, bovine and recombinant lactoferrins independently of their origins.

The composition of the present invention may comprise only one type of lactoferrin and conalbumin or two types.

The composition of the present invention is to be orally administered. Its form may be a pharmaceutical

The composition of the present invention may be administered singly or used together with other drugs. Further, the composition of the present invention can be added to a food and a feed in administtation.

The composition of the present invention is preferably made into pharmaceutical preparations in a dry state. Lactoferrin (hereinafter lactoferrin is explained as the central figure but the same can be said when other active ingredients are used) of a representative active ingredient of the composition of the present invention is unstable at high temperature and high humidity. More specifically, the amino group of lactoferrin can cause amino-carbonyl reaction with a reducing group present in the fillers or the like. Through many stages, this reaction leads to the formation of a brown dye by irreversibly polymerizing the reaction products (browning reaction). The presence of a substance which catalyzes oxidation and high temperatures accelerate this reaction. Namely, in making lactoferrin into pharmaceutical preparations, if water is present, the amino-carbonyl reaction can be accelerated by the influence of Fe^{3+} or the like present in lactoferrin. Further, the heat generation to be caused by tableting further accelerates this reaction as well. Thus, in order to obtain stable lactoferrin pharmaceutical preparations which maintain the pharmacological effect, the pharmaceutical preparations should be made in a dry state as much as possible.

Since the lactoferrin powder as such cannot be

base which has resistance to the gastric juice and dissolves in the small intestine, for example, a base to be selected from the group consisting of shellac, zein, hydroxypropylmethyl-cellulose phthalate, carboxymethylethylcellulose, cellulose acetate phthalate, a methacrylic acid copolymer, water-insoluble methylethylcellulose and an aminoalkyl methacrylate copolymer or a lubricant is added to granules containing the active ingredient to effect tableting and the obtained tablets may be coated with the film.

Particularly, the present inventors have confirmed lactoferrin in the blood of persons orally administered with enteric coated tablets of lactoferrin. Such knowledge could not have been obtained with the conventional tablets having lactoferrin as an active ingredient. The form of enteric coated preparations having lactoferrin as an active ingredient is one of preferred embodiments of the present invention. Furthermore, the form of enteric coated formulations which are made in the dry state and, simultaneously, have lactoferrin as an active ingredient is one of particularly preferred embodiments of the present invention.

The administration of enteric coated tablets of lactoferrin and the collection of blood were performed according to the following schedule. Namely, after eating breakfast at 7:00, the blood before administration of lactoferrin was collected a little before 9:30 (Pre-sampling), and enteric coated tablets of lactoferrin

(Preparation Example 5) were administered at 9:30, and then the blood was collected at 13:30 and 17:30 (4 hr-sampling and 8 hr-sampling, respectively) (Figure 12B).

Whether the prepared composition is enteric or not can be confirmed by testing its disintegrable properties with the use of a first solution (pH 1.2, General Testing Method 41 of the Pharmacopoea Japonica) obtained by adding 4 ml of diluted hydrochloric acid and water to 2.0 g of sodium chloride to dissolve it to form a solution of 1,000 ml and a second solution (pH 6.8) obtained by adding 118 ml of 0.2 N sodium hydroxide test solution and water to 250 ml of 0.2 M calcium dihydrogenophosphate to dissolve it to form a solution of 1,000 ml. When the tablets or granules which do not disintegrate on immersion in the first solution for 120 minutes but disintegrate on immersion in the second solution for 60 minutes do not dissolve in the stomach and start disintegration for the first time on flowing into the duodenum to elute the active ingredient, they can be judged enteric.

The composition of the present invention can exhibit an effect of improving the lipid profile in blood. On account of this, the composition of the present invention can be used in treating hypercholesterolemia, hyper-neutral lipidemia, hyper-low density lipoprotein (LDL) choleste-rolemia and hypo-high density lipoprotein (HDL) choleste-rolemia.

Further, the composition of the present invention can be also used in treating obesity, fatty liver and

Five point five kilograms of lactoferrin, 8 kg of lactose, 10 kg of crystalline cellulose, 1 kg of carboxymethylcellulose calcium, and 0.5 kg of a glycerin fatty acid ester were thoroughly mixed and subjected to dry granulation in the same manner as in Example 1, and then the resulting granules were pressure-molded into tablets each tablet containing 50 mg of lactoferrin and having a diameter of 8 mm and a weight average of 250 mg.

Preparation Example 3

Six kilograms of conalbumin, 10 kg of corn starch, 8.8 kg of hydroxypropylcellulose and 0.2 kg of magnesium stearate were mixed, and subjected to dry granulation in the same manner as in Example 1, and then the granules were pressure-molded into tablets each tablet containing 50 mg of conalbumin and having a diameter of 8 mm and a weight average of 250 mg

Preparation Example 4

Ten kilograms of spray dried egg white powder (a content of conalbumin of 8.4%), 10 kg of potato starch, 0.5 kg of silica gel were mixed in a dry state, and pressure-molded in the same manner as in Example 2, and then the disk was pulverized to collect particles having a particle diameter of not greater than 0.1 mm which was then pressure-molded into a tablet having a diameter of 10 mm and a weight average of 800 mg.

Preparation Example 5 (Preparation of Enteric Coated Tablet of Lactoferrin)

Five point five kilograms of lactoferrin, 8 kg of

lactose, 10 kg of crystalline cellulose, 1 kg of carboxymethylcellulose calcium and 0.5 kg of a glycerin fatty acid ester were mixed and subjected to dry granulation in the same manner as in Example 1, and then the granules were pressure-molded into tablets each containing 50 mg of lactoferrin and having a diameter of 8 mm and a weight average of 250 mg. These tablets were placed in a coating machine (Hicoater HCT-48N, manufactured by Freund Industry Co., Ltd.), and sprayed with a fluid obtained by dissolving 30 parts of shellac and 7 parts of castor oil into 63 parts of isopropanol in a calculated amount to produce tablets provided with 10%, based on the weight of the tablets, of enteric coating.

Example 1

Sixteen ICR line male mice of 5 weeks old were randomly classified into two groups of 8, and a control group was bred with a standard feed for rat and mouse (CE-2, a product of Japan Crea Co., Ltd.), and the other group was bred with CE-2 added with 1% lactoferrin (a product of Tatua Milk Biologix, in New Zealand, purity 84%) for four weeks. During this time, body weight was measured every three days, and with the lactoferrin group the body weight increased at a slightly quicker rate compared to the control group but there was no significant difference between both groups. Further, there was no significant difference in the weight of the liver, pancreas, spleen, small intestine, cecum, visceral fat, epididymal fatty tissue and the like which weighed on dissection after four

possibility is that the absorption of lipid in the digestive tract is inhibited. Then, the lipid of the liver where the absorbed dietary fat is stored was measured.

The liver removed from a mouse after four weeks was homogenized with a 2.5 M sucrose-containing phosphate buffer (ph 7.4), and the ground product was added with a mixed solvent of chloroform : methanol (2 : 1) to extract lipid, and cholesterol and neutral fat were measured. By adding 1% of lactoferrin to the standard feed CE-2, the cholesterol content of the liver was reduced by 21.7% ($P<0.01$) and the neutral fat content was reduced by 41.8% ($P<0.05$) compared to the control group (Figure 4). In other words, it was assumed that the action of lactoferrin to improve the blood lipid profile could be brought about by the lactoferrin which inhibited the absorption of dietary fat in the digestive tract. It is not known that lactoferrin inhibits the absorption of dietary fat by the digestive tract to improve lipid metabolism and reduces energy intake to exhibit a weight reduction effect as well, and this is a fact which the present inventors have elucidated for the first time.

Example 2

A male aged 42 took nine enteric coated tablets of lactoferrin (Preparation Example 5) dividedly in three parts after copious drinking (about 500 ml of whisky) (that is, nine tablets a day, equally divided into three parts at rising, before lunch and at bedtime, respectively).

Day 2 after the drinking, the neutral fat level was reduced to the normal region or in its neighborhood. When the enteric coated tablets of lactoferrin were not taken, the neutral fat level was over 200 mg/dl even day 7 after the drinking (Figure 5).

Example 3

Eight persons having a high total cholesterol level each continuously took nine enteric coated tablets of lactoferrin (Preparation Example of 5) a day, dividedly in three parts.

After about one month, with six persons having a total cholesterol level of a little higher than the normal level out of eight persons, the total cholesterol level was reduced ($P<0.01$ in Student's t-test) but with two persons whose total cholesterol level was in the normal region, the variation of the total cholesterol level was not recognized (Figure 6). From this fact, it can be considered that lactoferrin reduces only the cholesterol unnecessary for a human. Further, the collection of blood was performed at a scheduled time (around 11:00 a.m.).

Example 4

Twelve able-bodied females continuously took three to nine enteric coated tablets of lactoferrin (Preparation Example 5) a day for about one to two months. During this period, guidance in meals and exercise was not particularly given.

With most persons, the reduction in waist and the reduction in weight were recognized.

Example 5

A male drinker (a large bottle of beer and one double whisky every day) aged 37 took enteric coated tablets of lactoferrin (Preparation Example 5). At the beginning, the male took nine tablets, dividedly in three parts a day but felt sleepy and could not work, and thus on and after day 2, the male changed to take three tablets at bedtime.

When the neutral fat level was measured day 8, it was significantly reduced. Day 14, the cholesterol level was also reduced (Figure 8). This male had taken mevalotin for a long time but the total cholesterol level was reduced to 210 mg/dl for the first time. During this period, the dietary life was not particularly changed. Further, the collection of blood was performed before lunch.

Example 6

A female aged 43 having a high neutral fat level and a high total cholesterol level took nine enteric coated tablets of lactoferrin (Preparation Example 5) dividedly in three parts day 1 and day 2, three tablets at bedtime day 3, and six tablets, three tablets at rising and before bedtime, respectively, on and after day 4.

Day 12, the total cholesterol level was reduced to 231 mb/dl (Figure 9). The body weight was also reduced by 2 kg. During this period, the dietary life is not particularly changed. The collection of blood was performed between 10:00 a.m. and 11 a.m.

Example 7

Due to hyper-triglyceride(TG)-mia, a female aged 41 had taken lipantil for a several months. However, since impaired liver function had appeared, the female stopped taking lipantil and was provided with intravenous injections of Strong Minophargen for six days. The liver function was stabilized but the neutral fat level started rising again.

On starting taking lactoferrin enteric coated tablets of lactoferrin (preparation Example 5) (nine tablets, dividedly in three parts), the neutral fat level was 183 mg/dl at the beginning, and reduced to 153 mg/dl the next day. Further, the total cholesterol level which had not been reduced to 200 mg/dl or less without talking lipantil was reduced to 122 mg/dl day 7 (Figure 10). During this period, there was no particular change in the dietary life. The collection of blood was performed between 9:00 a.m. and 10 a.m.

Example 8

A female aged 65 who was not particularly obese took enteric coated tablets of lactoferrin.

This female only showed a total cholesterol level as high as 250 mg/dl or more and recently had slightly high neutral fat with ages. By taking mevalotin, the total cholesterol level was reduced but due to the side effect of a cramp in the foot or the like, it was impossible to take mevalotin.

On starting taking enteric coated tablets of

lactoferrin (Preparation Example 5) (nine tablets, dividedly in three parts), day 10, the total cholesterol level came to the 240 mg/dl level (Figure 11). During this time, there was no change in the dietary life. The collection of blood was performed between 10:00 a.m. and 11 a.m.

Example 9

A male drinker aged 42 (about 200 to 300 ml of whisky on an average of once every three to four days) took nine enteric coated tablets of lactoferrin (Preparation Example 5) dividedly in three parts a day.

When the neutral fat level and the total cholesterol level in the collected blood were measured about three times a day, a clear reduction in the total cholesterol level was recognized, and with the neutral fat level, a reducing trendency was observed as the whole although varied depending on days (variation due to meals) (Figure 12). Further, the neutral fat level the next morning after the drinking (shown by ● in Figure 12) was high but the neutral fat level was quickly reduced after discontinuing drinking.

Example 10

The lactoferrin concentration in blood on oral administration of enteric coated tablets of lactoferrin was measured by the ELISA method using an anti-bovine lactoferrin antibody.

Measurement of Lactoferrin by ELISA Method

1. Anti-bovine lactoferrin antibody (Goat, anti-bovine

20-PBS. Furthermore, 2,2-azino-bis(3-ethyl-benzothiazoline-6-sulfonic acid diammonium salt (1.18 M, a product of Sanko Pure Chemical Co., Ltd.) dissolved in a phosphate buffer was introduced to the plate in an amount of 100 µl/well as a substrate solution to effect reaction at 37°C for one hour.

7. The absorbance at a wavelength of 405 nm was measured by a microplate reader (Sunrise Series, Type Classic, manufactured by Chican Co., Ltd.), and the lactoferrin concentration was calculated from the calibration curve prepared at standards.

When 18 enteric coated tablets of lactoferrin (900 mg/60 kg=15 mg/kg) (Preparation Example 5) were administered to a male weighing 60 kg, the presence of lactoferrin was confirmed in the blood collected after four hours and eight hours (Figure 13A).

Administration and collection of blood were performed according to the following schedule. Namely, after eating breakfast at 7:00, the blood before the administration of lactoferrin was collected a little before 9:30 (Pre-sampling), and enteric coated tablets of lactoferrin (Preparation Example 5) was administered at 9:30, and then the blood was collected at 13:30 and 17:30 (4 hr-sampling and 8 hr-sampling, respectively) (Figure 13A).

Example 11

With a group of 11 persons administered with enteric coated tablets of lactoferrin (Preparation Example 5) and

CLAIMS

1. A composition for improving lipid metabolism having at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient.

2. A composition for treating at least one disease or condition to be selected from the group consisting of hypercholesterolemia, hyper-neutral lipidemia, hyper-low density lipoprotein (LDL) cholesterolemia, hypo-high density lipoprotein (HDL) cholesterolemia, obesity, fatty liver and cholesterol gallstone which has at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient.

3. A composition for treating a disease or condition for which the improvement of basal metabolic rate is to be effective which has at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient.

4. The composition of any one of claims 1 to 3 which is in the form of a dusting powder, a powder, a granule, a tablet or a capsule and can be obtained by the steps comprising mixing the active ingredient with pharmaceutically acceptable additives in the dry state; if desired, subjecting the mixture to strong pressure molding in the dry state and successively forming the molded product into fine particulates or granules of a uniform size; and tableting or encapsulating the mixture, the fine particulates or granules.

5. The composition of any one of claims 1 to 4 which is in the form of an enteric coated preparation.

6. The composition of any one of claims 1 to 4, wherein tableted granules containing the active component is coated with a film having, as the major component, a base which has resistance to the gastric juice and dissolves in the small intestine.

7. The composition of any one of claims 1 to 6 which is for the administration of the active ingredient in an amount of about 0.1 mg to about 50,000 mg, preferably about 0.5 mg to about 10,000 mg, more preferably about 10 mg to about 2,000 mg a day.

8. A method for producing a composition of any one of claims 1 to 7, said composition comprising the steps of mixing the active ingredient with pharmaceutically acceptable additives in the dry state; if desired, subjecting the mixture to strong pressure molding in the dry state and successively forming the molded product into

fine particulates or granules of a uniform size; and tableting or encapsulating the mixture, the fine particulates or granules, said composition being in the form of a dusting powder, a powder, a granule, a tablet or a capsule.

9. Use of at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient in producing a drug for improving lipid metabolism.

10. Use of at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient in producing a drug for treating at least one disease or condition to be selected from the group consisting of hypercholesterolemia, hyper-neutral lipidemia, hyper-low density lipoprotein (LDL) cholesterolemia, hypo-high density lipoprotein (HDL) cholesterolemia, obesity, fatty liver and cholesterol gallstone.

11. Use of at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising

peptides corresponding to lactoferrcin and lactoferricin of conalbumin as an active ingredient in producing a drug for treating a disease or condition for which the improvement of basal metabolic rate is to be effective.

12. The use of any one of claims 9 to 11, wherein the drug is in the form of a dusting powder, a powder, a granule, a tablet or a capsule and can be obtained by the steps comprising mixing the active ingredient with pharmaceutically acceptable additives in the dry state; if desired, subjecting the mixture to strong pressure molding in the dry state and successively forming the molded product into fine particulates or granules of a uniform size; and tableting or encapsulating the mixture, the fine particulates or granules.

13. The use of any one of claims 9 to 12, wherein the drug is in the form of an enteric coated preparation.

14. The use of any one of claims 9 to 12, wherein the drug is obtained by coating tableted granules containing the active ingredient with a film having, as the main component, a base which has resistance to the gastric juice and dissolves in the small intestine.

15. The use of any one of claims 9 to 14, wherein the drug is for the administration of the active ingredient in an amount of about 0.1 mg to about 50,000 mg, preferably about 0.5 mg to about 10,000 mg, more preferably about 10 mg to about 2,000 mg a day.

16. The use of any one of claims 9 to 15, wherein the drug is in the form of a dusting powder, a powder, a

granule, a tablet or a capsule and can be obtained by the steps comprising mixing the active ingredient with pharmaceutically acceptable additives in the dry state; if desired, subjecting the mixture to strong pressure molding in the dry state and successively forming the molded product into fine particulates or granules of a uniform size; and tableting or encapsulating the mixture, the fine particulates or granules.

17. A method of improving lipid metabolism comprising using at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient.

18. A method of treating at least one disease or condition to be selected from the group consisting of hypercholesterolemia, hyper-neutral lipidemia, hyper-low density lipoprotein (LDL) cholesterolemia, hypo-high density lipoprotein (HDL) cholesterolemia, obesity, fatty liver and cholesterol gallstone comprising using at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient.

19. A method of treating a disease or condition for

which the improvement of basal metabolic rate is to be effective comprising using at least one kind to be selected from the group consisting of a lactoferrin group protein comprising lactoferrin and conalbumin and an enzymatically decomposed product of the lactoferrin group protein comprising peptides corresponding to lactoferricin and lactoferricin of conalbumin as an active ingredient.

20. The method of any one of claims 17 to 19, wherein the active ingredient is used in the form of a dusting powder, a powder, a granule, a tablet or a capsule which can be obtained by the steps of mixing the active ingredient with pharmaceutically acceptable additives in the dry state; if desired, subjecting the mixture to strong pressure molding in the dry state and successively forming the molded product into fine particulates or granules of a uniform size; and tableting or encapsulating the mixture, the fine particulates or granules.

21. The method of claim 20, wherein the active ingredient is in the form of an enteric coated preparation.

22. The method of claim 20, wherein the active ingredient is obtained by coating tableted granules containing the active ingredient with a film having, as the main component, a base which has resistance to the gastric juice and dissolves in the small intestine.

23. The method of claim 21 comprising administering the active ingredient in an amount of about 0.1 mg to about 50,000 mg, preferably about 0.5 mg to about 10,000 mg, more preferably about 10 mg to about 2,000 mg a day.